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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

BRISTOL-MYERS SQUIBB COMPANY, Plaintiff, v. APOTEX INC. and APOTEX CORP., Defendants.	Civil Action No. 3:10-cv-05810 (MLC) (LHG) (consolidated with Civil Action No. 3:11-cv-6918 (MLC) (LHG))

APOTEX INC. AND APOTEX CORP.'S OPENING CLAIM CONSTRUCTION BRIEF PURSUANT TO L. PAT. R. 4.5

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Apotex Inc. and Apotex Corp. ("Apotex" or "Defendants") submit their Opening Claim Construction Brief for the asserted claims of the patents-in-suit.[1]

I. INTRODUCTION.

This is a Hatch-Waxman case where Apotex seeks to make a product that contains the drug dasatinib. Plaintiff Bristol-Myers Squibb ("BMS") asserts four patents here. The four patents fall into two categories.

The first, involving the '746, '875, and '856 patents, claims priority to the same provisional patent application, No. 60/129,510, filed April 15, 1999. These patents share a similar specification for claim construction purposes.[2] With this patent family, BMS preempted hundreds of billions of compounds and compositions for treating protein tyrosine kinase-associated disorders or cancers. Collectively, these are the Molecule patents. The second involves the fourth patent, the '725 patent. The '725 patent originates from patent application No. 11/192,897, filed July 29, 2005. The '725 patent includes certain monohydrate crystals of compounds, including dasatinib. (Docket Item ("D.I. 1-5"), '725 patent at col. 48, l. 48 – col. 50, l. 38).

The Molecule patents. The claim construction disputes between the parties involving the Molecule patents are a consequence of BMS's original attempt to claim broadly due to its uncertainty of what would be the final marketed compound. With the benefit of hindsight, BMS tried to craft narrower claims. But for the compound-related disputed terms, BMS is bound by the express structures, formulas and/or selection criteria that appear in the claims as-issued, which do not cover dasatinib. Other claim construction disputes for the Molecule patents (*e.g.*,

[1] The term "patents-in-suit" refers to U.S. Patent Nos. 6,596,746 ("the '746 patent"), 7,125,875 ("the '875 patent"), 7,153,856 ("the '856 patent"), and 7,491,725 ("the '725 patent").

[2] Apotex does not concede or agree that BMS has made a proper claim of priority, or that BMS can otherwise rely on the filing date of the provisional patent application to avoid prior art.

"salt," drug-resistant tumors) result from BMS's over-claiming or indefinite claiming. Finally, there are disputes relating to certain method step elements, such as "administering to."

The '725 Monohydrate patent. The claim construction disputes between the parties on the monohydrate patent pertain to the scope of the phrase, "crystalline monohydrate of the compound," the use of "compound" in dependent claims, and indefinite analytical test language.

II. LEGAL STANDARDS OF CLAIM CONSTRUCTION.

The claim construction inquiry begins with the plain and ordinary meaning of the claims, which define the scope of the right to exclude. *See Vitronics Corp.* v. *Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). "When construing patent claims, there is a heavy presumption that the language in the claim carries its ordinary and customary meaning amongst artisans of ordinary skill in the relevant art at the time of the invention." *Housey Pharm., Inc. v. Astrazeneca UK Ltd.*, 366 F.3d 1348, 1352 (Fed. Cir. 2004) (citation and internal quotation marks omitted); *see also Phillips* v. *AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005) (en banc) (general preference for "ordinary and customary meaning," that is "the meaning that the term would have to a person of ordinary skill in the art"); *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979-80 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996).

A patentee may sidestep the "ordinary and accustomed meaning … if the patentee has chosen to be his or her own lexicographer by clearly setting forth an explicit definition for a claim term." *Johnson Worldwide Assocs., Inc. v. Zebco Corp.*, 175 F.3d 985, 990 (Fed. Cir. 1999); *see also Astrazeneca AB v. Mut. Pharm. Co.*, 384 F.3d 1333, 1339 (Fed. Cir. 2004) (lexicography does not require rigid formalism or a specification that says, "I define __ to mean"). The specification may also reveal that a patentee has disavowed or relinquished claim scope. *See SciMed Life Sys., Inc.* v. *Advanced Cardiovascular Sys., Inc.*, 242 F.3d 1337, 1341 (Fed. Cir. 2001) ("Where the specification makes clear that the invention does not include a

particular feature, that feature is deemed to be outside the reach of the claims of the patent, even though the language of the claims ... might be considered broad enough to encompass the feature in question."); *Astrazeneca*, 384 F.3d at 1340 (specification that "describes a feature of the invention … and criticizes other products … that lack that same feature, this operates as a clear disavowal"); *Network, LLC v. Centraal Corp.*, 242 F.3d 1347, 1352 (Fed. Cir. 2001) ("The claims are directed to the invention that is described in the specification; they do not have meaning removed from the context from which they arose.").

The prosecution history can also reveal definitions and excluded claim scope. *Phillips*, 415 F.3d at 1317. A patentee cannot recapture in litigation subject matter surrendered during patent prosecution, either by amendment or argument. *See Pharmacia & Upjohn Co. v. Mylan Pharm., Inc.*, 170 F.3d 1373, 1376-77 (Fed. Cir. 1999); *see also Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1576 (Fed. Cir. 1995) ("Claims may not be construed one way in order to obtain their allowance and in a different way against accused infringers."); *Rheox, Inc. v. Entact, Inc.*, No. 98-03731 (MLC), 2000 WL 34540133, at *7 (D.N.J. Aug. 21, 2000) ("The prosecution history 'limits the interpretation of claim terms so as to exclude any interpretation that was disclaimed during prosecution.'" (quoting *Southwall*, 54 F.3d at 1576)).

III. THE ASSERTED PATENT CLAIMS.

Of the Molecule patent claims, BMS asserts claims 6, 7, 18, 27-30, 32, 33, 42-44, and 46-48 of the '746 patent; claims 1-3, 5, 7, 9-12, 14, and 27 of the '875 patent; and claim 1 of the '856 patent. From the '725 monohydrate patent, BMS asserts claims 1-16. Since the asserted Molecule patent claims are extraordinarily lengthy, the asserted claims are listed in full in Appendix A hereto. The terms presented for the Court's construction are listed in Appendix B hereto.

IV. PERSON OF ORDINARY SKILL.

Apotex's brief is directed to constructions of the disputed claim terms and phrases discussed below from the perspective of one of ordinary skill in the art at the time of the invention. The appropriate definition for each patent family is set forth in Apotex's expert declaration submissions. (Fernandez ¶ 17; Desiraju ¶ 16).[3] While the parties' definitions differ, Apotex does not believe that the differences are material to the claim construction disputes here.

V. ANALYSIS OF CLAIM TERMS IN DISPUTE.

The parties filed their Joint Claim Construction and Prehearing Statement on March 2, 2012. (D.I. 51). In Section A, below, Apotex analyzes the Molecule patents' claim terms. In Section B, below, Apotex analyzes the Monohydrate patent's disputed terms.

A. Claim Terms of the Asserted '746, '875, and '856 Patents.

The '746 patent has three independent claims: claim 6 (a compound or salt thereof, with a lengthy list of chemical names), claim 7 (a method of treating certain disorders comprising administration of a compound), and claim 43 (a compound or salt thereof having the structure shown). Claims 18, 27-30, 32, and 33 depend from claim 7; claim 42 depends from claim 6; and claims 44 and 46-48 depend directly or indirectly from claim 43.

The '875 patent has five independent claims: claims 1 and 3 (methods of treating cancer by administering a compound of formula III or salt thereof); and claims 2, 11, and 27 (methods of treating cancer by administering a compound of formula IV or salt thereof). Claims 5 and 7 depend directly or indirectly from claim 3; claim 9 depends directly from claim 1; claim 10 depends directly from claim 2; and claims 12 and 14 depend directly from claim 11.

The '856 patent has only one independent claim, claim 1, which is directed to a method

[3] References to "Fernandez ¶ __" refer to the Declaration of Ariel Fernandez submitted concurrently herewith. Similarly, references to "Desiraju ¶ __" refer to the Declaration of Gautham R. Desiraju submitted concurrently herewith.

for treating cancer by administering a compound having the structure shown therein.

The above claims contain various combinations of the terms in dispute. For example, claim 6 of the '746 patent uses the terms "salt," "compound," "selected from a group consisting of" and a chemical name. Claim 43 of the '746 patent uses the terms "salt" and "compound," and presents a chemical structure. Apotex addresses each term individually, but the applicable combined construction for each claim is set forth in Appendix B.

1. "Compound" (All asserted independent claims of '746 patent, '875 patent and '856 patents, and dependent claim 42 of '746 patent).

Chemical compounds generally have a defined set of atoms, arranged in a defined chemical structure, that are held together by bonds. BMS proposes construing "compound" as its "plain meaning," without further explanation. Apotex proposes construing the term to reflect the specification's express lexicography statements, so the term includes prodrugs, solvates, salts and stereoisomers of any particularly listed compound or structure.

For example, the specification expressly states the term "compound" encompasses salts:

> Compounds of the formula I may in some case form salts which are also within the scope of this invention. *Reference to a compound of the formula I herein is understood to include reference to salts thereof*, unless otherwise indicated.

(D.I. 1-2, '746 patent at col. 6, ll. 17-20; D.I. 1-3, '875 patent at col. 6, ll. 40-43; D.I. 1-4, '856 patent at col. 6, ll. 32-35) (emphasis added). This is a definitional statement that any compound of a given formula will necessarily encompass its salts. The specification similarly instructs that "[p]rodrugs and solvates of the compounds of the invention are also contemplated herein.... All stereoisomers of the present compounds ... are contemplated within the scope of this invention." (D.I. 1-2, '746 patent at col. 7, ll. 1-12; D.I. 1-3, '875 patent at col. 7, ll. 26-37; D.I. 1-4, '856 patent at col. 7, ll. 17-28).

Thus, the term "compound" should conform to the specification's clear statement that the

term encompasses "salts"; "prodrugs and solvates of the compound[]"; and "stereoisomers of the ... compound[]" or salt thereof.

2. "Salt" (all independent claims of the '746 patent, '875 patent (except claims 2 and 3), and the '856 patent).

All the asserted independent claims in the '746 patent, '856 patent (except claims 2 and 3), and '875 patent expressly use the claim language "salt." (*See* D.I. 1-2, '746 patent at col. 276, l. 53, col. 297, l. 41, col. 302, l. 19; D.I. 1-3, '875 patent at col. 276, l. 54, col. 278, l. 42, col. 282, l. 3; D.I. 1-4, '856 patent at col. 278, l. 67). The parties dispute the scope of what qualifies as a salt.

Apotex seeks a construction of "salt" that conforms to the specification definition:

> The term "salt(s)", as employed herein, denotes acidic and/or basic salts formed with inorganic and/or organic acids and bases. Zwitterions (internal or inner salts) are included within the term "salt(s)" as used herein (and may be formed, for example, where the R substituents comprise an acid moiety such as a carboxyl group). Also included herein are quaternary ammonium salts such as alkylammonium salts. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are useful, for example, in isolation or purification steps which may be employed during preparation.

(*See, e.g.*, D.I. 1-2, '746 patent at col. 6, ll. 21-31) (emphasis added). BMS proposes excluding the underlined text from the definition of "salt," stating that the deletion of the underlined text is consistent with the "[p]lain meaning as understood by a person of ordinary skill in the art." (D.I. 51, Joint Claim Construction and Prehearing Statement, Ex. B, at 1, 5, 16, 27, 31).

The specification expressly states that zwitterions "are included within the term 'salt(s)'" and that quaternary ammonium salts are "[a]lso included herein." That is the epitome of lexicography. Apotex thus requests a construction that reflects—and is essentially a quotation of—the salt definition the purported inventors gave. BMS offers no grounds for excluding them.

3. "*A compound* or salt thereof *selected from the group consisting of*." ('746 patent, independent claim 6).

Claim 6 of the '746 patent recites, "A ***compound*** or salt thereof ***selected from the group consisting of***: [a lengthy list of almost 550 specific chemical names]." (D.I. 1-2, '746 patent at col. 276, l. 53 – 297, l. 37) (emphasis added). Apotex contends this language precludes mixtures of the listed compounds and other compounds not part of the list, including impurities. BMS contends such mixtures are so permitted by the claims.

Claim 6 of the '746 patent is structured as a "Markush claim," (*see* Manual of Patent Examining Procedure ("MPEP") § 803.02), and as such, it uses the closed transitional phrase "selected from the group consisting of." "The transitional phrase 'consisting of' excludes any element, step, or ingredient not specified in the claim." (MPEP § 2111.03). Thus, the plain claim language necessarily excludes anything other than one compound expressly recited in the Markush group. The presence of any other compound on the list, or compounds not explicitly listed in claim 6, is outside the claim scope.

Apotex relies on the claim construction reasoning of "a ... selected from the group consisting of" in *Abbott Labs. v. Baxter Pharmaceutical Products, Inc.*, 334 F.3d 1274, 1280-81 (Fed. Cir. 2003). In *Abbott*, the Federal Circuit noted that the use of "a" in conjunction with a Markush grouping must be construed to exclude mixtures, including a mixture of compounds within the Markush group list itself. *Id*. at 1281 ("'a' with 'consisting of' in this case indicates only one member of a Markush group.... If a patentee desires mixtures or combinations of the members of the Markush group, the patentee would need to add qualifying language while drafting the claim" such as "and mixtures thereof" or "at least one member of the group"). Here, there is no qualifying "mixtures thereof" or "at least one" language in claim 6.

Thus, Apotex respectfully submits that to fall within the scope of claim 6, there can be

one, and only one, compound from the compound name list. Any substance that mixes two compounds on the list (whether or not as an impurity), or mixes one compound on the list and one off the list, is outside the scope of this claim language.

4. The chemical name "'N-(2-Chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxy ethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazole-carboxamide." ('746 patent, independent claim 6).

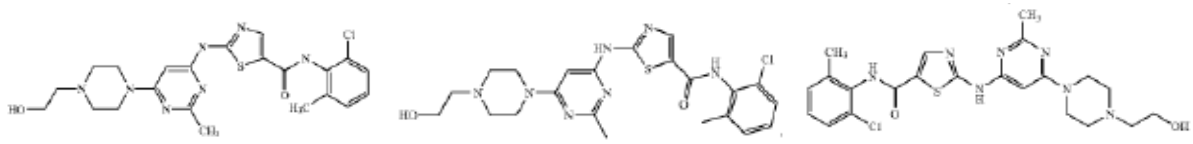
Claim 6 of the '746 patent also is directed to "A compound or salt thereof selected from the group consisting of [a list of almost 550 chemical names]," one of which is "'N-(2-Chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazole carboxamide." (D.I. 1-2, '746 patent at col. 276, l. 53 – col. 297, l. 37, *in particular* at col. 292, lines 46-48). Apotex proposes this complicated chemical language be given the meaning it would have under established chemical nomenclature rules. BMS seeks to expand this claim language in order to have it cover dasatinib by proffering what it terms "equivalent" structures to the claim language. (D.I. 51, Joint Claim Construction and Prehearing Statement, Ex. B, at 2).

Nothing in the '746 patent suggests that the chemical nomenclature identified should be given any meaning besides the plain and ordinary meaning of chemical nomenclature, as understood by those of ordinary skill in the art. The specification provides no additional direction or special instructions for interpreting chemical nomenclature as a whole, or individual components within the chemical name. No particular relevant nomenclature term was at issue during prosecution. Thus, the chemical name presumptively has its ordinary meaning. *See Housey*, 366 F.3d at 1352 ("there is a heavy presumption that the language in the claim carries its ordinary and customary meaning amongst artisans of ordinary skill in the relevant art at the time of the invention." (citations and internal quotation marks omitted)).

The plain and ordinary meaning of these chemical names is apparent to one of ordinary skill in the art. Those of skill in the art recognize the benefits of employing a consistent

nomenclature practice in naming chemical compounds. (Fernandez ¶ 23). Particularly where the compounds involved are complex or have many substituent groups, strict adherence to nomenclature rules is essential in order to ensure clarity and consistency in the work of those of skill in the art. (*Id.*) To that end, the International Union of Pure and Applied Chemistry ("IUPAC") has developed the standard for chemical nomenclature worldwide. (Fernandez ¶ 24). IUPAC periodically publishes materials which are widely recognized as providing the standard against which nomenclature practices are interpreted ("the IUPAC Guidelines"); the IUPAC Guidelines provide a formulaic way of naming chemical compounds that accurately and consistently describes the chemical structure, including all substituent groups. (Fernandez ¶ 24-25; *see also* Shannon Decl., Ex. A,[4] A GUIDE TO IUPAC: NOMENCLATURE OF ORGANIC COMPOUNDS (1993) (APO(Das)025796-026000)). In short, a person of skill would refer to and apply the IUPAC Guidelines to correlate a chemical name to a compound structure, including the chemical names recited in claim 6.[5] (Fernandez ¶ 26). Apotex's construction thus simply asks this Court to respect the specific chemical names the purported inventors specified as falling within claim 6.

BMS proposes construing the chemical name as meaning three "equivalent structures"':



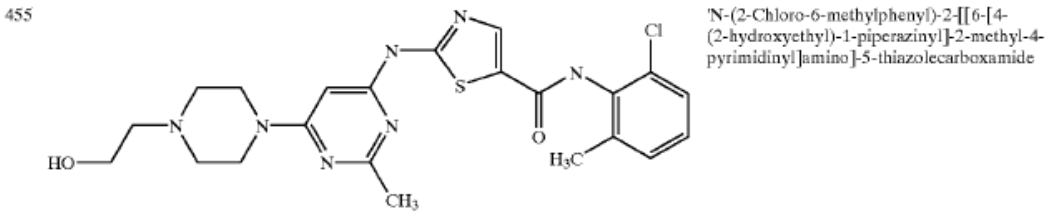
(D.I. 51, Joint Claim Construction and Prehearing Statement, Ex. B, at 2). Not coincidentally, BMS includes dasatinib's structure as "equivalent", but dasatinib *would not result if the chemical*

[4] References to "Shannon Decl., Ex. __" refer to the Declaration of Luke T. Shannon submitted concurrently herewith.

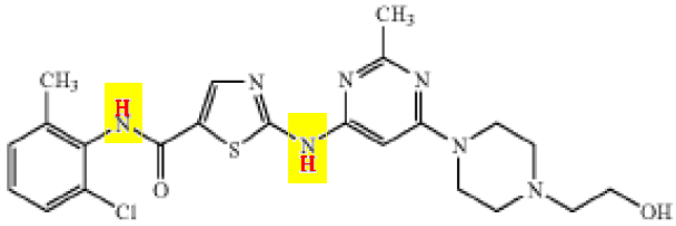
[5] Apotex does not admit that the chemical names identified in claim 6 comply with the IUPAC Guidelines to the letter, but instead recognizes that the purported inventors at points deviate from IUPAC Guidelines in their use of the chemical names of claim 6.

nomenclature rules are applied using their ordinary meaning. Since the chemical language means what it means under the nomenclature rules, to the extent BMS wants to propose that dasatinib is "equivalent" to the claimed nomenclature, that is an issue for the element-by-element comparison in the infringement analysis; claims cannot be expanded during claim construction.

BMS's proposed construction for at least the two rightmost structures is at odds with the specification itself. BMS in its joint statement points to the '746 patent at cols. 213-214, Example 455, as supposedly correlating the chemical name in claim 6 to the following structure:



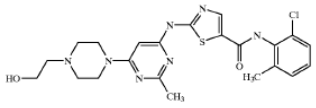
Example 455's structure is not dasatanib. Dasatinib has two additional hydrogen (H) atoms bound to two nitrogen (N) atoms in the Example 455 structure (emphasis added):



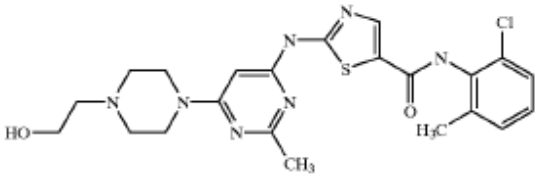
(D.I. 51, Joint Claim Construction and Prehearing Statement, Ex. B, at 2). Thus, even under BMS's intrinsic evidence source for claim meaning, dasatinib is outside the claim scope.

Nevertheless, claim 6 was drafted to use chemical nomenclature, instead of a graphic, to describe various compound structures. Claim 43 of the '746 patent, discussed next, did use the Example 455 graphical description to define the compound claimed. Thus, at this stage, there is no reason to erase those distinct claiming approaches that BMS chose of its own volition. Thus, if this Court seeks to construe the chemical language, it can simply instruct that the claim 6

chemical nomenclature as having its plain and ordinary meaning, according to standard IUPAC nomenclature guidelines, and further note that the term excludes dasatinib.

5. The compound  **('746 patent claim 43; '856 patent claim 1).**

While claim 6 of the '746 patent used chemical language in the claim, claim 43 of the '746 patent and claim 1 of the '856 patent deliberately chose to use a graphical approach, reciting:

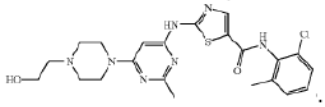
43. The compound 

including salts thereof.

(D.I. 1-2, '746 patent at col. 302, ll. 9-20; *see also* D.I. 1-4, '856 patent at col. 278, ll. 53-67). This structural representation is what it is: a compound with an expressly defined chemical structure.

BMS seeks to effectively rewrite the claims, by first asserting that the claimed structure corresponds to a particular chemical name, then asserting that the appropriate conversion of that chemical name back into a structure yields the dasatinib structure:

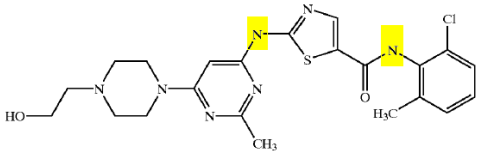
The compound represented by 'N-(2-Chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide, and is the same as



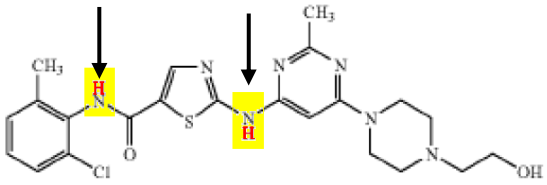
(D.I. 51, Joint Claim Construction and Prehearing Statement, Ex. B, at 6, 13). The replacement structure BMS proposes for claim 43 suffers from the same problem noted above for claim 6: it has added two new hydrogen atoms and bonds to two of the nitrogen atoms. That is improper

claim redrafting, which cannot be done during the claim construction phase. *Helmsderfer v. Bobrick Washroom Equip., Inc.*, 527 F.3d 1379, 1383 (Fed. Cir. 2008) ("Courts cannot re-write claim language."); *K-2 Corp. v. Salomon S.A.*, 191 F.3d 1356, 1364 (Fed. Cir. 1999) ("Courts do not rewrite claims; instead, we give effect to the terms chosen by the patentee.").

BMS's alternative argument for adding two hydrogen atoms to the claimed structure is that the person of ordinary skill in the art would have understood that the presence of hydrogen atoms is implicit in the structure. One of skill in the art would *not* assume that the structure in the claims can be substituted with two more bonds and two new hydrogen atoms *on the nitrogen atoms*. (Fernandez ¶ 42). Rather, one of skill in the art would expect that if hydrogen atoms were meant to fill those bonds, the structure of this term would have shown hydrogen atoms at those locations. (Fernandez ¶ 46). To the extent there is a convention in organic chemistry to not show hydrogen atoms, it is in the context of *carbon* atoms, not nitrogen atoms, since the number of bonds carbon can form is always fixed at four. (Fernandez ¶ 36). Here, BMS is not adding hydrogen atoms to carbons; it is adding them to bridging nitrogen (N) atoms:



Claim 43 structure



BMS's proposed revised structure

(*Compare* D.I. 1-2, '746 patent at col. 302, ll. 9-20, *and* D.I. 1-4, '856 patent at col. 278, ll. 53-67, *with* D.I. 51, Joint Claim Construction and Prehearing Statement, Ex. B, at 6, 13) (emphasis added).

If BMS wants to argue the two structures depicted above are equivalent, it can try to do so during the element-by-element part of the infringement analysis. It is not the proper purpose for a claim construction analysis. Indeed, since BMS recognizes that dasatinib is not "exactly"

within the claimed structure, if anything the structure should be construed to exclude dasatinib.

Thus, Apotex respectfully requests that this Court construe this compound graphic claim language to mean, "A compound with the structure expressly identified in the claim, wherein this structure cannot represent a compound known as dasatinib."

6. "Administering to"; "A subject in need thereof" ('746 patent independent claim 7, dependent claims 44 and 47; '875 patent independent claims 1-3, 11, 27; and '856 patent independent claim 1).

Claims 7, 44, and 47 of the '746 patent, claim 1 of the '856 patent, and claims 1-3, 11, and 27 of the '875 patents are all directed to methods that include the step of "***administering to***" "***a subject in need thereof***" a compound having the structure shown in those claims. Apotex's constructions of these terms reflects the understanding of one of ordinary skill in the art.

a. "A subject in need thereof" ('746 patent claims 7, 44, 47; '875 patent claims 1-3, 11, 27; '856 patent claim 1).

The obvious prerequisite to administering the disclosed compounds to "a subject in need thereof" is that the subject must be known to require such treatment. *See, e.g.*, *Jansen v. Rexall Sundown, Inc.*, 342 F.3d 1329, 1331-33 (Fed. Cir. 2003) (construing "a method of treating … macrocytic-megaloblastic anemia in humans ... which comprises administering a daily oral dosage of a vitamin preparation to a human in need thereof" as language that requires that the "need" for therapy be recognized and appreciated, and that the compound must be intentionally administered for treatment of the recited condition); *Schering Corp v. Glenmark Pharm. Inc.*, No. 07-1334 (JLL), 2008 WL 4307189, at *9 (D.N.J. Sept. 16, 2008) (finding that the phrase "'in need of such treatment' ... has intent written into it" and requires an intent to use the drug for the purpose for which it was intended). Thus, the phrase "***a subject in need thereof***" requires both a subject and a person who has diagnosed that subject as "in need thereof."

The specification describes the "subjects": "Preferred subjects for treatment include animals, most preferably mammalian species such as humans, and domestic animals such as

dogs, cats and the like, subject to protein tyrosine kinase-associated disorders." (D.I. 1-2, '746 patent at col. 26, ll. 53-57; D.I. 1-3, '875 patent at col. 30, ll. 1-4; D.I. 1-4, '856 patent at col. 29, ll. 56-59). All are included.

The specification also explains who will be "in need thereof." The '746, '875 and '856 patents identify the field of the inventions as including "methods of using [the disclosed] compounds in treating protein tyrosine kinase-associated disorder such as immunologic and oncologic disorders, and to pharmaceutical compositions containing such compounds." (D.I. 1-2, '746 patent at col. 1, ll. 9-14; D.I. 1-3, '875 patent at col. 1, ll. 13-17; D.I. 1-4, '856 patent at col. 1, ll. 16-20). The patents purport to "provide[] methods for the treatment of protein tyrosine kinase-associated disorders, comprising the step of administering to a subject in need thereof at least one compound of" the formula disclosed in the patents. (D.I. 1-2, '746 patent at col. 23, ll. 28-32; D.I. 1-3, '875 patent at col. 26, ll. 32-36; D.I. 1-4, '856 patent at col. 26, ll. 32-36).

One of ordinary skill in the art thus would understand that the claims are directed to compounds that purportedly can be used for the treatment of protein tyrosine kinase-related disorders. Thus, one of ordinary skill in the art would understand that a "subject in need thereof" *must* be someone suffering from a protein tyrosine kinase-related disorder. Knowing whether a person is suffering from such a disorder depends entirely on whether a physician, clinician, etc., has diagnosed the person as such. Indeed, it beggars belief to suppose that one of ordinary skill in the art would understand "a subject in need thereof" to mean someone who has not been diagnosed with a protein tyrosine kinase-related disorder, as such disorders are not readily apparent absent a diagnosis by a clinician.

The claim language also explicitly requires the step of administering "to" a subject "in need" of treatment. This means that two separate people are required to perform the method

steps: person A will give the product for the stated remedial purpose, while person B will be the person "in need" of such treatment, to whom the product is administered.

Thus, this phrase should be construed to mean, "Any living organism having a protein-kinase associated disorder known to be susceptible to treatment with [the compound(s), as construed above], as diagnosed by a second party, likely a physician or other clinician."

b. "Administering to" ('746 patent claims 7, 44, 47; '875 patent claims 1-3, 11, 27, '856 patent claim 1).

i. "Administering" refers to Administration Alone or in Combination; In a Single Dose or Divided Doses.

The specification is clear that administering the therapeutic agent can occur either alone or in combination with other therapeutic agents, in a single dose or in divided doses:

> Other therapeutic agents such as those described below may be employed with the inventive compounds in the present methods. In the methods of the present invention, such other therapeutic agent(s) may be administered prior to, simultaneously with or following the administration of the compound(s) of the present invention.

(D.I. 1-2, '746 patent at col. 23, ll. 32-37; D.I. 1-3, '875 patent at col. 26, ll. 36-41; D.I. 1-4, '856 patent at col. 26, ll. 36-41). The specification also states that doses of the compound "may be administered in a single dose or in the form of individual divided doses, such as from 1 to 4 times per day." (D.I. 1-2, '746 patent at col. 26, ll. 39-45; D.I. 1-3, '875 patent at col. 29, ll. 54-60; D.I. 1-4, '856 patent at col. 29, ll. 42-48). Apotex's construction simply reflects specification's expansive teachings without introducing extraneous or other limiting elements into the claim term. Thus, administering should be construed to include administration either alone or in combination with other therapeutic agents, where the claimed compounds are administered either "prior to, simultaneously with or following administration of" the other therapeutic agents, as well as in a single or divided dose.

ii. Two Actors Required.

The phrase "***administering to***" requires two actors: a first person who gives the therapeutic agent in question—the administrating actor—and a second "subject" who is in need of treatment—the receiving actor. The word "to," in the context of this term, makes this clear. *See Eastman Kodak Co. v. Goodyear Tire & Rubber Co.*, 114 F.3d 1547, 1553 (Fed. Cir. 1997), *abrogated on other grounds by Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448 (Fed. Cir. 1998), (construing the word "to" by "examin[ing] principally the claim language and any syntactic signs of its meaning"). If the word "to" is to have any meaning at all, it must mean that both an administering and a receiving actor are required in order to meet this claim limitation.

The claim language supports Apotex's construction. The claim term that follows "administering to" makes clear that the compound is administered to "a subject in need thereof," discussed above. In context, construing the claims to require only a single actor makes no sense. The specification does not envision that the patient population will be limited to practicing oncologists self-administering. Since the specification envisions a treatment population that includes animals, (D.I. 1-2, '746 patent at col. 26, ll. 53-57; D.I. 1-3, '875 patent at col. 30, ll. 1-4; D.I. 1-4, '856 patent at col. 29, ll. 56-59), who cannot administer drugs to themselves, two actors are required.

To the extent BMS attempts to suggest its claims were intended to cover single-party acts, the Federal Circuit has had little sympathy for such arguments, since a patentee:

> can usually structure a claim to capture infringement by a single party.... BMC could have drafted its claims to focus on one entity. The steps of the claim might have featured references to a single party's supplying or receiving each element of the claimed process…. BMC chose instead to have four different parties perform different acts within one claim…. [T]his court will not unilaterally restructure the claim or the standards for joint infringement to remedy these ill-conceived claims. *See Sage Prods. Inc. v. Devon Indus. Inc.*, 126 F.3d 1420, 1425 (Fed. Cir. 1997) ("[A]s between the patentee who had a clear opportunity to negotiate broader claims but did not do so, and the public at large, it is the patentee who must bear the cost of its failure to seek

protection for this foreseeable alteration of its claimed structure.").

BMC Res., Inc. v. Paymentech, L.P., 498 F.3d 1373, 1381 (Fed. Cir. 2007). BMS drafted these claims; it must live with their clear meaning.

Thus, Apotex respectfully submits that the "administering to" language be construed to require two actors: one, the subject in need of treatment; two, another person, likely a physician, nurse practitioner or other clinician, responsible for giving the therapeutic agent in question.

7. "Wherein the cancer is resistant to treatment by STI-571." ('875 patent claims 9, 10, 12, 27).

Claims 9, 10, 12, and 27 of the '875 patent are each directed to methods for the treatment of cancer "***wherein the cancer is resistant to treatment by STI-571***." If this term is to have any meaning, it must be construed to require both a subject in need of cancer treatment and a second person who has diagnosed the cancer as resistant to STI-571.

The '875 patent makes clear what this claim term is intended to cover: "The compounds of the present invention are also useful in the treatment of cancers that are sensitive to and resistant to chemotherapeutic agents that target BCR-ABL and c-KIT, such as, for example, Gleevec® (STI-571)." (D.I. 1-3, '875 patent at col. 28, ll. 35-38). One of skill in the art would recognize that STI-571 refers to the compound generally known as imatinib, which the '875 patent identifies as a chemotherapeutic agent used in the treatment of cancer. (*See id.*).

The only way to know whether this limitation is met is to know beforehand that the subject at issue suffers from a cancer that is sensitive to and resistant to STI-571. Case law supports this conclusion. *See, e.g.*, *Jansen*, 342 F.3d at 1331-33 (construing claims to require that the "need" for therapy be recognized and appreciated, and that the compound must be intentionally administered for treatment of the recited condition); *Schering*, 2008 WL 4307189, at *9 (finding that the phrase "'in need of such treatment' ... has intent written into it" and

requires an intent to use the drug for the purpose for which it was intended). The knowledge as to whether the cancer being treated is resistant to STI-571 can only be gathered where the subject to be treated has determined that said subject suffers from such a cancer.

A cancer patient will not know whether that cancer is or is not resistant to imatinib unless and until a physician or other clinician has reached such a conclusion. Absent the prior verification that the cancer is imatinib-resistant—which would be the logical result if this claim is capable of being infringed by a single actor—one would have no idea whether treatment by administration of the claimed compound infringes these claims, or how that person could adjust his or her activities to avoid infringement. Rather than providing clarity to the parties and to potential infringers, such a construction introduces additional uncertainty and a lack of notice.

Thus, Apotex respectfully submits that this phrase be construed to require two actors: one, the subject in need of treatment; two, another person, likely a physician or other clinician who has determined that said cancer in patient is resistant to treatment by STI-571; wherein STI-571 is known as Gleevec™ (imatinib mesylate).

B. Claim Terms of the '725 Monohydrate Patent.

The '725 monohydrate patent differs from the Molecule family of patents in that its claims pertain to a particular three-dimensional monohydrate crystal structure associated with dasatinib. The asserted independent claims are claims 1, 3, and 12.

1. "Crystalline monohydrate of the compound of formula (IV)." ('725 patent claims 1, 3, 12).

Claims 1, 3, and 12 of the '725 patent are directed to "***[c]rystalline monohydrate*** of the compound of formula (IV)" that reflects specified results upon analytical testing. (D.I. 1-5, '725 patent at col. 48, ll. 48-60; *id*. at col. 49, ll. 1-13; *id*. at col. 50, ll. 12-24). This "crystalline monohydrate" term has a general meaning, which is then modified given the intrinsic evidence.

Ordinary meaning. Judge Posner, sitting by designation, succinctly explained the nature

of drug crystal forms in *SmithKline Beecham Corp. v. Apotex Corp.*, 247 F. Supp. 2d 1011 (N.D. Ill. 2003), *rev'd on other grounds*, 403 F.3d 1331 (Fed. Cir. 2005). A drug is "polymorphous" when the same substance "appear[s] in more than one crystalline form." *Id*. at 1016. In these different crystal forms, the drug "molecules are the same," but the crystal lattice framework in which they sit in three-dimensional space is different. *Id*. These differences in crystal structure "can affect the melting point ... and other properties of the crystal, such as hardness." *Id*. "Because a different arrangement of molecules implies a different pattern of bonds, and different bonds vibrate at different frequencies, different polymorphs of the same chemical [also] produce different x-ray diffraction patterns and infrared spectra, which are two types of graphic mapping of the atomic forces binding the crystal." *Id*.

Drug crystals can also exist with "their molecules arranged differently" and "a slightly different molecular composition." *SmithKline*, 247 F. Supp. 2d at 1016. One such crystal type "is a solvate, which is a crystal in which molecules of a solvent, such as water, have become 'caught' inside the crystal and have bonded with the other molecules in an altered crystalline structure. When the trapped and bonded solvent is water, the solvate is called a hydrate." *Id*. at 1016-17. The descriptive type of hydrate depends upon its water-to-drug ratio. Thus, "a hydrate in which there is one water molecule for every two of the other molecules constituting the unit crystal cell ... the hydrate is called a *hemihydrate*." *Id*. at 1017. When a crystal has a 1:1 ratio of water-to-drug in the unit cell, the crystal is called a *monohydrate*, as the PTO recognized here:

> In the instant case, **Claim 20** is limited to a monohydrate and **Claim 27** is limited to one molecule of water per molecule of Formula IV. *They are claiming the same thing*.

(Shannon Decl., Ex. B, '725 patent Prosecution History ("PH"), 9/18/07 Office Action, at 6 (APO(Das)016395) (underline and italics added)).

Thus, one of ordinary skill in the art typically understands "crystalline" to mean a solid product that is made up of crystals, with molecules arranged in a repeating fixed unit cell lattice structure. (Desiraju ¶ 21). As the unit cells repeat themselves, that creates long-range order, which in turn produces crystallinity. (*Id.*). Crystals with water molecules complexed within their unit cell in the crystal lattice are called "hydrates," and exhibit different properties (*e.g.*, x-ray powder diffraction patterns). (Desiraju ¶ 22; Shannon Decl., Ex. C, STEDMAN'S MEDICAL DICTIONARY 838 (27th ed. 2000) (defining "hydrate" as "[a]n aqueous solvate (in older terminology, a hydroxide); a compound crystallizing with one or more molecules of water") (APO(Das)026011); *see also* Shannon Decl., Ex. D, CHURCHILL'S ILLUSTRATED MEDICAL DICTIONARY 880 (1989) (APO(Das)026029)).

The specification. The '725 patent does not suggest that it originally was intended to describe crystalline monohydrates. The title and abstract of the specification state the "invention relates to processes for preparing compounds" of a more general formula, "and crystalline forms thereof." (D.I. 1-5, '725 patent, Abstract). This latter aspect, "and crystalline forms thereof," was a later addition to the '725 patent's application, which was originally filed as a patent application directed towards only processes for preparing compounds. (Shannon Decl., Ex. E, Provisional Application Serial No. 60/542,490 (APO(Das)018172-225); *see also* D.I. 1-5, '725 patent at Related U.S. Application Data). Not until BMS filed a later continuation-in-part application was new matter added to the specification to discuss particular crystal polymorphs of dasatinib that BMS had found would result from following those process conditions.

Further, the '725 patent is quite particular about the methodologies that can be used to prepare the "crystalline monohydrate of the compound of formula (IV)." (*See* D.I. 1-5, '725 patent at col. 43, l. 30 – col. 44, l. 22). It is clear to a person of ordinary skill in the art reading

the specification that the particular processes that BMS originally sought to patent were what prompted the monohydrate crystal formation.[6] (Desiraju ¶ 25).

The "crystalline monohydrate" language also conveys to the person of ordinary skill reading the specification that the subject matter of the invention is a stand-alone, raw material substance, and not a mixture, for at least three reasons. ***First***, to the extent the '725 patent claims envision drug mixtures, it is in the context of drug + excipients in pharmaceutical compositions, in separate dependent claims. *See Leibel-Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 910 (Fed. Cir. 2004) ("the presence of a dependent claim that adds a particular limitation raises a presumption that the limitation in question is not found in the independent claim."); *see also Wenger Mfg., Inc. v. Coating Mach. Sys., Inc.*, 239 F.3d 1225, 1233 (Fed. Cir. 2001) ("Claim differentiation ... is clearly applicable when there is a dispute over whether a limitation found in a dependent claim should be read into an independent claim, and that limitation is the only meaningful difference between the two claims."). ***Second***, the specification states that "[t]he present invention also provides using the compounds obtained with the inventive process to *further* prepare pharmaceutical compositions." (D.I. 1-5, '725 patent col. 31, ll. 33-35 (emphasis added); *see also id*. at col. 31, l. 35 – col. 32, l. 53). In this context, the inventive processes produce a raw material, which can be further used to prepare pharmaceutical compositions. ***Third***, the analytical test results called for by the claims can only "substantially" conform to the figures if they are raw material samples. (Desiraju ¶ 37).

The phrase "crystalline monohydrate ..." also as a whole has a narrow meaning when applied to "the compound of formula (IV)" claim language for many of the same reasons

[6] Apotex reserves the right to argue that this claim term, or any other claim term discussed herein, is invalid for any reason, including but not limited to written description, indefiniteness, enablement, and written description under 35 U.S.C. § 112.

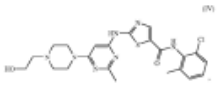
discussed in Federal Circuit decision in *Abbott Labs. v. Sandoz, Inc.*, 566 F.3d 1282 (Fed. Cir. 2009). In *Abbott*, the Federal Circuit affirmed the district court's construction of the term "crystalline" to mean "Crystal A as outlined in the specification." *Id*. at 1289-91. The Federal Circuit explained that this was appropriate because only a specific crystal, called "Crystal A," was identified as the invention; only Crystal A was capable of producing the analytical test results set forth in the specification and claims; and the only product capable of being produced by the allegedly inventive processes was "Crystal A." *Id*.

Prosecution history. During prosecution, the PTO Examiner rejected the pending claims in view of the prior art disclosures in the Molecule patents and elsewhere that recognized the compounds in this class would be expected to form hydrates and solvates. (Shannon Decl., Ex. B, '725 patent PH, 9/18/07 Office Action, at 3-5 (APO(Das)016392-94)). BMS argued back that the prior art "does not disclose that the compound of formula IV, as a monohydrate, would exist in crystalline form," or exist "as a one water molecule to one water molecule of the compound," and that there was "no expectation [from the prior art] that the compound of formula IV would form a crystalline monohydrate." (Shannon Decl., Ex. F, '725 patent PH, 12/18/07 Amendment and Response, at 6 (APO(Das)016411)).

In response, the PTO stated that this detailed structural information and lack-of-expectation assertion meant BMS was entitled "only to the crystalline forms that are adequately described in the specification and are not entitled to a generic crystalline claim...." (Shannon Decl., Ex. G, '725 patent PH, 3/3/08 Office Action, at 4 (APO(Das)016420)). This further limits BMS to just crystals that are produced by the specification's procedures.

Proposed Construction: Thus, the term "crystalline monohydrate of the compound of formula (IV)" should be construed to mean, a raw material produced by process conditions

presented in the specification, with a particular arrangement of the following compound structure

 in three dimensional space that has a certain degree of long range order, with a 1:1 molar arrangement of water to compound formally associated in a unit crystal cell lattice. Apotex's proposed construction is the only construction supported by the ordinary meaning and intrinsic evidence as understood by one of ordinary skill in the art.

2. "Wherein the compound is substantially pure." ('725 patent claims 8, 15, 16).

Claims 8, 15, and 16 of the '725 patent depend directly or indirectly from either claim 3 or 12 and include the term, "wherein the compound is ***substantially pure***." In the context of these claims, "purity" does not apply and cannot be understood.[7]

The term "substantially" is an imprecise modifier. "Definiteness problems often arise" when such imprecise modifiers are used in a claim, creating invalidity issues under 35 U.S.C. § 112. *Seattle Box Co. v. Industrial Crating & Packing, Inc.*, 731 F.2d 818, 826 (Fed. Cir. 1984). Patentees are permitted to use such words of degree so long as the person of ordinary skill in the art, or the patent's specification, has "*some standard* for measuring that degree." *Id.* (emphasis added); *see also Verve, LLC v. Crane Cams, Inc.*, 311 F.3d 1116, 1119-20 (Fed. Cir. 2002) (court must assess whether those skilled in the art had an accepted meaning for "substantially"). BMS points to language such as the following at col. 15, lines 27-56 as the standard:

> As used herein, "substantially pure" means a compound having a purity greater than 90 percent, including 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, and 100 percent. As one example, a crystalline form of the compound of the formula (IV) can be substantially pure in having a purity greater than 90 percent, where the remaining less than 10 percent of material comprises other form(s) of the compound of the formula (IV), and/or reaction

[7] Indefiniteness need not be addressed at this early claim construction stage. Nevertheless, Apotex has identified the issue, but does not waive the right to raise the defense.

and or processing impurities arising from its preparation….

(D.I. 1-5, '725 patent at col. 15, ll. 28-40; *see also* D.I. 51, Joint Claim Construction and Prehearing Statement, Ex. B, at 42, 51, 52). This creates more problems than it solves.

A "compound" is "a substance formed by the covalent or electrostatic union of two or more elements, generally differing entirely in physical characteristics from any of its components." (Shannon Decl., Ex. C, STEDMAN'S MEDICAL DICTIONARY 392 (27th ed. 2000) (APO(Das)026009)). A compound structure thus cannot be 90%, or 99% pure; it is what it is. In the specification text above, an "example" appears to be discussing a raw material sample, but the correct way to describe that is to describe the *bulk drug substance* as substantially pure. This would require rewriting the claim language, which is impermissible. It would also be necessary to state the units of purity, *e.g.*, purity by weight percent, volume percent, molar percent, all of which will change the nature of what is in or out of the claims and are routine purity measures used in the pharmaceutical industry. (Desiraju ¶ 73). If the term was intended to apply to a pharmaceutical composition, it still makes no sense since "desired excipients" are not considered to be impurities in a pharmaceutical composition. *See Glaxo Grp. Ltd. v. Apotex, Inc.*, 376 F.3d 1339, 1347 (Fed. Cir. 2004) ("excipients are not considered to be impurities").

Further, the "substantially" language also cannot work if it is intended to describe compound purity *within* the monohydrate crystal. A monohydrate crystal structure mandates 50% drug compound, 50% water compound, and nothing else in the crystal structure. If water is not deemed an impurity, there is nothing else present in the monohydrate crystal. Removing 90% or more of the water is incompatible with a "monohydrate"; a crystal that is 100% drug compound with no water, for example, is an *anhydrate*, not a monohydrate.

"In construing claims, the analytical focus must begin and remain centered on the

language of the claims themselves, for it is that language that the patentee chose to particularly point out and distinctly claim the subject matter which the patentee regards as his invention." *Honeywell Int'l, Inc. v. Int'l Trade Comm'n*, 341 F.3d 1332, 1338 (Fed. Cir. 2003) (internal quotation marks and alterations omitted). However, the Federal Circuit has made clear that if "a claim is not 'amenable to construction,' then the claim is invalid as indefinite under 35 U.S.C. § 112, ¶ 2." *Id*. "The definiteness requirement of § 112, ¶ 2 'focuses on whether the claims, as interpreted in view of the written description, adequately perform their function of notifying the public of the [scope of the] patentee's right to exclude.'" *Id*. (citing *S3 Inc. v. nVIDIA Corp.*, 259 F.3d 1364, 1371-72 (Fed. Cir. 2001)). Thus, where a claim is "insolubly ambiguous," and cannot be saved by a narrowing construction, that claim is invalid. *Id*. at 1338-39.

Apotex respectfully submits that the above claim language is insolubly ambiguous even with the understanding of the person of ordinary skill, and thus is indefinite.

3. "Which is characterized by an x-ray powder diffraction pattern substantially in accordance with that shown in FIG. 1." ('725 patent claim 1).

Claim 1 of the '725 patent is directed to a crystalline monohydrate of the compound shown "which is characterized by an x-ray powder diffraction pattern substantially in accordance with that shown in FIG. 1." Figure 1 was plainly invoked to allow one of ordinary skill to uniquely identify the referenced "crystalline monohydrate" by generating an x-ray powder diffraction ("XRPD") pattern that matches Figure 1. BMS asserts "substantially" is intended to account for measurement conditions and error that might lead, for example, to changes in peak intensity. However, this term must be construed to capture no more than the inventive crystal and specific compound required by the claims, or else this term is rendered meaningless.

BMS deliberately chose to claim one specific "crystalline monohydrate" and additionally invoke the XRPD "fingerprint" shown in Figure 1 of the '725 patent. (D.I. 1-5, '725 patent at

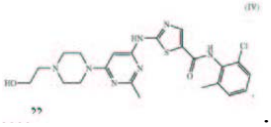
col. 48, ll. 62-63). *See Abbott*, 566 F.3d at 1287 (test method in claims is intended to "yield a unique 'fingerprint' for each crystalline form of a chemical"); *see also* Desiraju ¶¶ 31-32 (providing general overview of the methodology). However, as Judge Wolfson recognized in *Roche Palo Alto LLC v. Ranbaxy Labs. Ltd*, No. 06-2003, 2009 WL 3261252 (D.N.J. Sept. 30, 2009), it is not unusual for crystal forms share peaks in the same location of an x-ray pattern. *Id*. at *6-*8 (multiple crystal forms of drug and excipients produced peaks at 3.5 degrees 2-theta).

BMS, by suggesting at this stage that this Court can ignore, for example, peak order, peak intensity, and the like, is already seeking to expand the claims in an impermissible matter. *Compare Abbott Labs. v. Sandoz, Inc.*, 486 F. Supp. 2d 767 (N.D. Ill. 2007) (rejecting patentee's attempt to prove infringement using x-ray peaks that had shifted too far from the patent figures and claimed positions, or were so small that they represented little more than a small intensity or "shoulder"). This term must be construed such that the product being considered must *match* the data in Figure 1 in such a way as to uniquely identify the product being considered as "[c]rystalline monohydrate of the compound of formula (IV)." In general, therefore, even slight differences in an XRPD pattern can result in an inability to uniquely identify the substance being considered. (Desiraju ¶¶ 34-37).

Further, by suggesting that this term only requires an XRPD pattern that is "substantially identical" to Figure 1, BMS's proposed construction fails to recognize that if the XRPD pattern of a product being characterized deviates from Figure 1, one of ordinary skill in the art would lack confidence that the product being characterized is in fact the referenced "[c]rystalline monohydrate of the compound of formula (IV)." (Desiraju ¶ 37). Apotex's proposed construction comports with the claim 1 language and the understanding of one of ordinary skill. A meaning other than Apotex's deprives one of ordinary skill of the ability to identify the

specific "[c]rystalline monohydrate of the compound of formula (IV)," as required by claim 1.

Proposed Construction: Thus, Apotex respectfully requests this claim language be construed as, "The product being characterized must match the x-ray powder diffraction pattern presented in FIG. 1 of the patent specification, and further do so in such a way so as to uniquely identify the referenced '[c]rystalline monohydrate of the compound of formula (IV)



'"

4. "Which is characterized by an x-ray powder diffraction pattern (Cu k_α γ = 1.5418 Å at a temperature of about 23° C.) comprising four or more 2θ values selected from the group consisting of: 18.0±0.2, 18.4±0.2, 19.2±0.2, 19.6±0.2, 21.2±0.2, 24.5±0.2, 25.9±0.2, and 28.0±0.2." ('725 patent claim 3).

Claim 3 of the '725 patent is directed to the crystalline monohydrate of the compound of formula (IV) "which is characterized by an x-ray powder diffraction pattern (Cu k_α γ = 1.5418 Å at a temperature of about 23° C.) comprising four or more 2θ values selected from the group consisting of: 18.0±0.2, 18.4±0.2, 19.2±0.2, 19.6±0.2, 21.2±0.2, 24.5±0.2, 25.9±0.2, and 28.0±0.2." This claim language is exceedingly problematic.[8]

First, as noted in Section (B)(1) above, there is only one unique type of crystal that, based on BMS's representations to the PTO, can be covered by the claims: the one produced according to the specification procedures. This crystalline material purportedly has *all* of the peaks in the x-ray pattern listed above, *and many others*. Thus, the above claim language is redundant. *See Abbott*, 566 F.3d at 1289 (noting that defining "crystalline" as "Crystal A," where "Crystal A" incorporates seven PXRD peak limitations, arguably renders the claim to crystalline cefdinir with seven PXRD peaks redundant, and thus proceeding to narrow the claims further).

[8] Apotex raised indefiniteness and written description invalidity defenses to this claim language, but the analysis of this is better reserved for a later date; Apotex raises them to ensure non-waiver.

Second, the language "selected from the group consisting of" requires the presence of just these few peaks *and no others*. (*See* Section (A)(3) above for Markush group discussion). Thus, the claim language excludes the very crystal it is supposedly meant to characterize.

Third, to the extent BMS would suggest that a pattern need only have just the above few peaks, without tethering them to monohydrate Formula IV crystals, that creates the added problem that the claims could include other materials with peaks in these locations, but which have nothing whatsoever to do with the claimed compound (*e.g.*, impurities, excipients, other hydrate structures, etc.). This is nowhere justified in the written description support.

Fourth, even if one of ordinary skill could comprehend the claim, the numerical terms invoke "2θ values" that incorporate a variance of "±0.2." (D.I. 1-5, '725 patent at col. 49, ll. 18-19). The '725 patent specification nowhere provides support for such a wide variation in "2θ values," other than simply to list the values included in this limitation. (D.I. 1-5, '725 patent at col. 44, ll. 43-49). It also may be an overbroad range. *See Abbott*, 486 F. Supp. 2d at 772-73 (finding that ±0.1 was the appropriate scope for particular 2θ values, and that the ±0.2 range touted by Abbott's expert—the same expert BMS offers here—was overbroad).

Thus, Apotex respectfully submits this language is insolubly ambiguous.

5. "Characterized by unit cell parameters approximately equal to the following: Cell dimensions: a(Å)=13.8632(7); b(Å)=9.3307(3); c(Å)=38.390(2); Volume=4965.9(4) Å3 Space group Pbca Molecules/unit cell 8 Density (calculated) (g/cm3) 1.354." ('725 patent claim 5).

Claim 5 of the '725 patent is directed to "[t]he compound of claim 3," "[c]haracterized by unit cell parameters approximately equal to the following: Cell dimensions: a(Å)=13.8632(7); b(Å)=9.3307(3); c(Å)=38.390(2); Volume=4965.9(4) $Å^3$ Space group Pbca Molecules/unit cell 8 Density (calculated) (g/cm^3) 1.354." The precision required by this term is impossible in

anything but a specially-grown single crystal; there is no standard for "approximately equal."[9]

The type of data set forth in claim 5 is derived from what is known as a "single crystal." Single crystal analysis typically is done on specially-grown crystals made or identified specifically for analytical testing. (Desiraju ¶ 52). It is not a test routinely run on bulk pharmaceutical samples. Thus, although these values are very specific, one of ordinary skill in the art would know that these values are not supported by the specification. Claim 3, from which claim 5 depends, is drawn to a crystalline monohydrate of the compound of formula (IV) that is characterized by data obtained from XRPD (as discussed above), which is done on bulk samples, not single crystals. Even if XRPD could be used to determine unit cell parameters, one of ordinary skill in the art would not be able to confirm the unit cell parameters to the precision required by this term, which requires precision up to 0.0001 Å.[10] (Desiraju ¶ 53).

This term also requires the unit cell parameters to be "approximately equal to" the stated values. Yet, these words of degree are not given any standard in the specification, quantitatively or qualitatively, rendering them indefinite. *See Seattle Box*, 731 F.2d at 826 ("Definiteness problems often arise when words of degree are used in the claim.... When a word of degree is used the district court must determine whether the patent's specification provides some standard for measuring that degree."); *Datamize, LLC v. Plumtree Software, Inc.*, 417 F.3d 1342, 1351-53 (Fed. Cir. 2005) (finding the term "aesthetically pleasing" indefinite where the patentees failed to provide an objective standard for measuring that term); *Glaxo Grp. Ltd. v. Ranbaxy Pharm., Inc.*, 262 F.3d 1333, 1336 (Fed. Cir. 2001) (claim limitation "essentially free from crystalline material" did little by itself to "enlighten" the amount of crystalline material permitted within the

[9] Apotex raised indefiniteness and written description invalidity defenses to this claim language, and notes them so there is no waiver.

[10] The term "Å" refers to the unit angstrom, one ten billionth of a meter. (Desiraju ¶ 53).

scope of claim 1); *compare Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 1354-56 (Fed. Cir. 1998) ("substantially free" construed to include a numerical limitation in view of specification data). Nor is there an applicable industry standard here. *Compare Chimie v. PPG Indus., Inc.*, 402 F.3d 1371, 1375, 1378 (Fed. Cir. 2005) (term "dust-free" was alone indefinite, but industry standards could be used to give the term a meaning).

Thus, Apotex respectfully submits that this language is insolubly ambiguous, unsupported, and not capable of being construed.

6. "Which is characterized by differential scanning calorimetry thermogram and a thermogravimetric analysis substantially in accordance with that shown in FIG. 2." ('725 patent claim 2); "[Being further] characterized by a differential scanning calorimetry having a broad peak between approximately 95° C and 130° C"; "Wherein the differential scanning calorimetry further has a peak at approximately 287° C." ('725 patent claims 9, 11, 12).

Claim 2 of the '725 patent depends from claim 1 and is directed to "[t]he compound of claim 1, ***which is characterized by differential scanning calorimetry and a thermogravimetric analysis substantially in accordance with that shown in FIG. 2***." Claims 9, 11, and 12 of the '725 patent are directed to the "compound of claim 3" or "[c]rystalline monohydrate of the compound of formula (IV)," which is "characterized" by specified DSC "peaks." Claim 9 requires the "the compound" to be "characterized by a differential scanning calorimetry having a ***broad peak*** between ***approximately*** 95° C and 13° C"[11]; claim 11 depends from claim 9 and requires the DSC to "ha[ve] a ***peak*** at ***approximately*** 287° C"; and claim 12 requires that the crystalline monohydrate be "characterized by a differential scanning calorimetry having a ***broad peak*** between ***approximately*** 95° C and 130° C." (D.I. 1-5, '725 patent at col. 50, ll. 1-28). One of ordinary skill in the art would be unable to understand the meaning of these terms. Here

[11] Although this term of claim 9 purports to refer to a peak between "approximately 95° C and 13° C," a certificate of correction has yet to issue. Nevertheless, this term is addressed herein as it was considered by the examiner, namely as referring to "approximately 95° C and 130° C."

again, the parties' disputes involve analogous issues from those discussed in the prior sections.[12]

First, to understand and interpret the results of a DSC test, one of skill in the art must know the methodology used in carrying out the test, as test conditions and related variables affect the outcome. (Desiraju ¶ 44). Particularly for hydrated solids, there can be a significant difference in results depending on how the test procedure itself is performed (*e.g.*, open pan, closed pan, crimped pan with pinhole). (*Id.*; *see also* Shannon Decl., Ex. H, Stephen Byrn et al., *Pharmaceutical Solids: A Strategic Approach to Regulatory Considerations*, 12 PHARMACEUTICAL RES. 945, 950 (1995) ("DSC analysis of solvates [in the specific experiment described] should be carried out using either an open pan or a pan with a pin-prick; otherwise, unusual and variable resutls will be obtained because the solvent is not provided a way of escape from the pan….") (APO(Das)018461)). The patent *does not* provide the measurement protocol. This is a failure that renders the claims indefinite. *Honeywell*, 341 F.3d at 1336-40 (holding "that the claims are insolubly ambiguous, and hence indefinite, with respect to a required sample preparation method" because "[d]epending upon which sample preparation is used, the calculated MPE [required by the claims] for a given sample can vary greatly.").

Second, in claim 2, BMS asserts the person of ordinary skill can decide if the two test results are "substantially in accordance" with one another. (D.I. 51, Joint Claim Construction and Prehearing Statement, Ex. B, at 36). Apotex is concerned that BMS's refusal to tie the claims to the particular monohydrate crystal required by the claims and as set forth in the specification is designed to improperly expand the claims to cover other substances (*e.g.*, other hydrates, other compounds, other excipients) that may through happenstance produce similar peak results, giving rise to false positives. *See Roche*, 2009 WL 3261252, at *6-*8; *see also*

[12] Apotex has raised indefiniteness and written description invalidity defenses to this claim language; Apotex thus notes the issues to ensure non-waiver.

SmithKline, 247 F. Supp. 2d at 1039 (noting the risk of false positives as a consequence of similarly-structured polymorphs, because "[i]f you compared the sharp photograph of one person's fingerprints with a blurred photo of another person's fingerprints, you might conclude that they were the same person," leading to a false identification).

Third, claims 9, 11 and 12 refer to a DSC "peak," unlike claim 2, which properly describes the output of a DSC test result as a thermogram. DSC measures the amount of heat required to increase the temperature of the substance being tested. (Desiraju ¶ 43). The data generated by DSC tests reflect sample transitions (*e.g.*, melting point), and thus these events change the sample. (*Id*.) For this reason, those of ordinary skill in the art do not use the term "peak" to refer to DSC data outputs. Rather, those of ordinary skill understand DSC tests produce endothermic or exothermic transitions as shown in a thermogram. The use of the different claim language in claims 9, 11 and 12 presumably was deliberate, and intended to convey some different meaning relative to the DSC-related language in claim 2. *See Aspex Eyewear, Inc. v. Marchon Eyewear, Inc.*, 672 F.3d 1335, 1349 (Fed. Cir. 2012) (that different claims use different terms in parallel settings supports conclusion that the terms have different meanings); *Comark Comm'ns, Inc. v. Harris Corp.*, 156 F.3d 1182, 1187 (Fed. Cir. 1998) (different words in seaprate claims are presumed to have different meanings). BMS does not attempt to illuminate matters, asserting the "plain meaning" should apply or just re-using the term "peak." (D.I. 51, Joint Claim Construction and Prehearing Statement, Ex. B, at 44, 48, 49). But there is no "ordinary" understanding of a "peak" in the DSC context. Thus, claims 9, 11 and 12 are insolubly ambiguous.

Fourth, claims 9, 11 and 12 again use words of degree such as "broad peak," "approximately 95° C and 130° C," or "approximately 287° C," again without specification

guidance or standards. One of ordinary skill would not readily understand how to quantify the breadth of a peak being "broad," or the scope of what is "approximately" a peak in the varied locations, nor have the purported inventors provided such guidance in the patent. (Desiraju ¶ 60). Thus, for the same reasons noted in prior sections relating to claim language of degree, such terms are also insolubly ambiguous. (*See generally* cases cited in Section (B)(2), above).

7. "Which corresponds to the loss of one water of hydration on thermogravimetric analysis." ('725 patent claims 9, 12).

Claims 9 and 12 are directed to "the compound of claim 3" (claim 9) or crystalline monohydrate (claim 12), having "peaks" that "correspond[] to the ***loss of one water of hydration on thermogravimetric analysis***." Thermogravimetric analysis ("TGA") is a technique that measures change in the weight of a sample as a function of temperature. (Desiraju ¶ 66). Such a change might indicate to one of skill in the art that residual solvent, such as water, is lost, perhaps confirming the presence of that solvent. (*Id.*). Once again, however, the claim language takes what should be a straightforward concept (specifying a weight amount loss over a specified time or temperature, *see* Section (B)(8), below), to instead call for the use of the test to measure the "loss of one water of hydration on thermogravimetric analysis," which is not the output of the test method (especially if the sample tested contains other volatiles, such as adsorbed water or solvents). (*Id.*). This renders the claim language insolubly ambiguous.

Further, claim 9 directs that it is the "compound of claim 3" that is to lose one water of hydration. But the compound formula given in claim 3 is the Formula IV structure, which does not have a ready water molecule available to lose by thermogravimetric analysis measurements. To remove the OH and one extra H from the structure to make "H_2O" would require fundamentally altering the structure and producing a decomposition product. Claim 9 also refers both to characterization by DSC and "the loss of one water of hydration on thermogravimetric

analysis." (D.I. 1-5, '725 patent at col. 50, ll. 1-5). Whatever energy is needed to make a decomposition product of the Formula IV compound is not going to correlate to the energy needed to melt a monohydrate crystal. Nor can the same sample be tested first by TGA then by DSC or vice versa; one of ordinary skill in the art would understand that once *either* test is performed on a crystalline hydrate sample (assuming a crystalline sample would potentially fall within claim 9), the water molecules of the crystalline structure are lost forever. (Desiraju ¶ 68). It would not be possible to perform the tests serially, because the substance loses its water molecules after the first test and cannot be recreated for the second. (*Id*.).

For these reasons, this claim term is insolubly ambiguous and is therefore not capable of being construed.

8. "Which is further characterized by a weight loss of 3.48% by thermogravimetric analysis between 50° C and 175° C." ('725 patent claim 10).

Claim 10 of the '725 patent at least properly uses a more correct output description of the TGA test, namely a "weight loss of 3.48% by thermogravimetric analysis between 50° C and 175° C." The problem, however, is that the material that is supposedly supposed to lose the weight is "***the compound*** of claim 9." For the same reasons noted above for claim 9 in Section (B)(7) above, the ***compound*** structure of Formula IV is not going to lose water unless it is fundamentally changed. Thus, the plain meaning of the claim language seeks to describe an impractical, if not inoperable, circumstance.

Thus, this claim language also is insolubly ambiguous.

9. "A process for preparing the compound of claim 3." ('725 patent claim 6, 7).

Claims 6 and 7 of the '725 patent are directed to "[a] process for preparing the compound of claim 3" comprising heating, dissolving, and crystallizing steps and specifying various parameters. Apotex's construction simply follows the governing law and specifies that this term

requires any covered "process" to occur in the United States.[13]

The Patent Statute and Federal Circuit precedent make clear that acts that can constitute infringement of a process claim must occur in the United States in order to support infringement.[14] *See, e.g.*, 35 U.S.C. § 271(a); *Welker Bearing Co. v. PHD, Inc.*, 550 F.3d 1090, 1095 (Fed. Cir. 2008) (no infringement "until the product is used, sold, or offered for sale in the United States during the term of the patent"). Apotex's construction simply recognizes that reality. Thus, Apotex respectfully submits that clear, binding precedent requires construing this claim language to mean one that is U.S.-based.

10. "The compound of claim [1, 3, or 12]." ('725 patent claims 2, 4, 5, 8, 9, 10, 11, 13, 14, 15, 16).

Claims 2, 4, 5, 8-11, and 13-16 all purport to be directed to "***[t]he compound of***" independent claims 1, 3, or 12. BMS construes "the compound" language by parroting the underlying independent claim language of crystalline monohydrate of the compound of formula (IV). But that approach imports new limitations into the claim, which is improper. *E.I. Du Pont de Nemours & Co. v. Phillips Petroleum Co.*, 849 F.2d 1430, 1433-34 (Fed. Cir. 1988) ("[W]e know of no principle of law which would authorize us to read into a claim an element which is not present, for the purpose of making out a case of novelty or infringement. The difficulty is that if we once begin to include elements not mentioned in the claim in order to limit such claim and avoid a defense or anticipation, we should never know where to stop." (quoting *McCarty v. Lehigh Valley R. Co.*, 160 U.S. 110, 116, (1895))).

The specification distinguishes between a "crystalline monohydrate" and a "compound." It states "[t]he compound of formula (IV) ... is an inhibitor of SRC/ABL and is useful in the

[13] Apotex notes that this term refers to a process for preparing "the compound of claim 3" and for this reason is incapable of being construed for the reasons discussed in Section (B)(10), said discussion incorporated herein by reference.

[14] Minor exceptions exist, which are wholly inapplicable in this case.

treatment of oncological diseases." (D.I. 1-5, '725 patent at col. 1, ll. 51 – 65). The specification then elsewhere states that "another aspect" of the invention is "*crystalline forms* of the *compound* of formula (IV)." (D.I. 1-5, '725 patent at col. 4, ll. 55-56) (emphasis added). The '725 patent also purports to disclose a method for the preparation of *crystalline* monohydrate of formula (IV), where the *compound* of formula (IV) is listed as a starting material. (D.I. 1-5, '725 patent at col. 43, l. 30 – col. 44, l. 26). This reflects the reality that a compound of Formula IV can exist in multiple iterations (such as in solution) in a manner distinct from the monohydrate structure (since a monohydrate structure is a creature of the solid phase, not the liquid phase).

Thus, since the dependent claims referenced in this section expansively call for a Formula IV "compound" without restriction, they are invalid under 35 U.S.C. § 112, ¶ 4. *See Pfizer, Inc. v. Ranbaxy Labs. Ltd.*, 457 F.3d 1284, 1292 (Fed. Cir. 2006) (since dependent claim "fails to 'specify a further limitation of the subject matter' of the claim to which it refers" and covered subject matter "outside the scope of claim 2," asserted claim was invalid under § 112, ¶ 4).

VI. CONCLUSION.

For the reasons stated herein, Apotex respectfully requests that the Court adopt Apotex's proposed constructions of the disputed claim terms and phrases.

Respectfully submitted,

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